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Synthesis of (*E*)-β-iodo vinylsulfones *via* iodine-promoted iodosulfonylation of alkynes with sodium sulfinates in an aqueous medium at room temperature†

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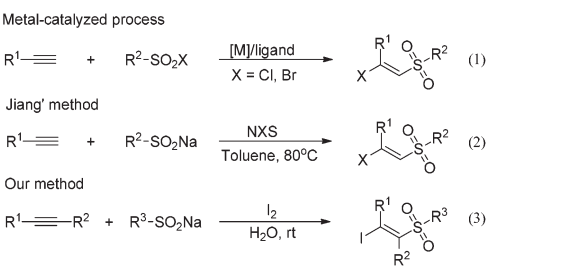
An efficient molecular iodine-promoted method for the synthesis of (*E*)-β-iodo vinylsulfones using water as the solvent at room temperature has been developed. This green reaction is fast, operationally simple, environmentally benign and, especially, proceeds under very mild conditions to afford the target products with high regio- and stereoselectivity.

The development of an environmentally benign and efficient protocol for the synthesis of privileged molecular skeletons has been a challenging task for synthetic chemists.[1] Among them, multi-component reactions (MCRs) in water have been shown to be a helpful toolkit in organic synthesis as well as for the requirements of green chemistry because of their convergence, operational simplicity, facile automation and relevant character.[2] Recently, radical cascades have become synthetically very attractive because they enable access to highly complex molecular frameworks in only a few synthetic steps. In addition, because of the excellent stereo and enantiocontrol in radical reactions, numerous highly stereoselective radical cascade processes have been developed over recent years.[3]

The formation of C–S bonds is one of the fundamental transformations in the synthesis of organosulfur compounds.[4] Halo vinylsulfones represent one particularly interesting organosulfur compound because both the vinyl halide and vinylsulfone moiety are important intermediates in organic chemistry. Vinylsulfone containing molecules have been found to be widespread in biological research, such as HIV-1 inhibitors,[5] cysteine protease inhibitors,[6] covalent protease inhibitors,[7] and inhibitors of a transpeptidase required for cell wall protein anchoring and virulence in *Staphylococcus aureus*.[8] Therefore, the development of a general method for constructing these frameworks has attracted considerable interest among organic chemists. Generally, transition metal-catalyzed addition of sulfonyl halogens to terminal alkynes has been considered to be the most powerful method to construct halo vinylsulfones (Scheme 1, eqn (1)).[9] Recently, Nakamura[10] and Li[11] demonstrated iron-catalyzed chlorosulfonylation of terminal alkynes with sulfonyl chloride and sulfonylhydrazides, respectively. Despite the efficiency of these reactions, the use of toxic metal greatly restricts the application of these reactions in areas of the pharmaceutical industry. More recently, Jiang and coworkers developed an elegant NBS or NIS-promoted difunctionalization of terminal alkynes to form β-halo vinylsulfones under metal-free conditions; unfortunately, this reaction also needs the toxic compound toluene as solvent (Scheme 1, eqn (2)).[12] Therefore, the development of green methods for the synthesis of β-halo vinylsulfones with high selectivity under mild reactions is still highly desirable. Herein we disclose a novel protocol for the preparation of β-iodo vinylsulfones through iodine-promoted tandem radical reactions involving C–S and C–I bond formation (Scheme 1, eqn (3)).

On the basis of recent development of iodine-mediated reactions[13] and new reactions for the formation of C–S bonds,[14] we envisioned that the multi-component reactions of terminal alkynes, sodium sulfinates and iodine would provide β-iodo vinylsulfones. To probe the feasibility of our assumption, we started our investigation by using phenylacetylene **1a**



Scheme 1 Synthetic approaches to halo vinylsulfones.

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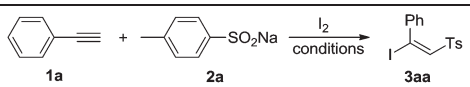
and sodium *p*-toluenesulfinate **2a** as model substrates under various conditions and the results are summarized in Table 1. To our delight, on treatment of phenylacetylene **1a** and sodium *p*-toluenesulfinate **2a** with iodine (1 equiv.) at room temperature in water for 2 h, the corresponding β-halo vinylsulfone **3aa** was obtained in 45% yield (Table 1, entry 1). Higher yields were obtained when **2a** was employed in excess amounts (2 equiv.) and the reaction time was prolonged from 2 to 4 h (Table 1, entries 2 and 3). Increasing the stoichiometry of iodine from 1 equiv. to 1.5 equiv. led to a significant increase in product yields (Table 1, entries 4 and 5). Next, the effect of the solvent on the reaction efficiency was examined (Table 1, entries 6–15). It was found that the solvent played a critical role in the success of this process. Among all the solvents tested, water was the most suitable solvent for the present transformation, possibly due to an intrinsically better solubility of the sodium *p*-toluenesulfinate in water. Thus, the optimal reaction conditions were **1a** (1 equiv.), **2a** (2 equiv.) and I_2 (1.5 equiv.) in water at room temperature for 2 h (Table 1, entry 4). The stereochemistry and precise configuration of β-iodo vinylsulfones were unambiguously confirmed by single-crystal X-ray analysis of **3aa** (Fig. 1).

With the above optimized conditions, a range of alkynes were tested to explore the scope of the substrates, and the results are summarized in Table 2. Generally, various aryl- and alkyl-substituted terminal alkynes were well tolerated under the reaction conditions and afforded the corresponding products in moderate to excellent yields. For the *para*-substituted phenylacetylenes, the electron-donating substituents (Et, *t*-Bu, MeO, and EtO) gave better reactivity than the electron-withdrawing substituents (F, Cl, and Br). The substituents in the *para* or *ortho* position did not affect the desired products yields, and **3ad** and **3ag** were obtained in 75% and 78% yields, respectively. It should be noted that the products (**3ad–3ag**) containing two carbon–heteroatom bonds enabled further modification to achieve more complex structures through sequential metal-catalyzed cross-coupling reactions. Furthermore, other heterocyclic alkynes such as 2-ethynylthiophene and 3-ethynylpyridine were also investigated and found to form the desired products in 91% and 82% yields, respectively. Moreover, the aliphatic terminal alkynes such as ethynylcyclopropane and hex-1-yne could also be successfully employed to afford the desired iodosulfonylation products **3am** and **3an** in 85% and 82% yields, respectively. To our delight, the internal alkynes can also be successfully transformed into the iodosulfonylation products **3ao–3ap** in moderate yields.

To expand the scope of this methodology, a series of sodium sulfinates were also employed to react with phenylacetylene under optimized conditions (Table 3). A variety of sodium benzenesulfinates, bearing electron-donating groups (Me, MeO) or electron-withdrawing groups (F, Cl, and Br) on the aryl ring, reacted smoothly with phenylacetylene, affording the corresponding β-iodo vinylsulfones **3ca–3ia** in good to excellent yields. Nevertheless, arylacetylenes bearing the same substituents at the *para*, *ortho*, and *meta* positions were also

Table 1 Optimization of reactions[a]



Entry	I_2 (equiv.)	**2a** (equiv.)	Solvent	Time (h)	Yield[b] (%)
1	1	1	H_2O	2	45
2	1	2	H_2O	2	55
3	1	2	H_2O	4	62
4	1.5	2	H_2O	2	86
5	1.5	2	H_2O	4	87
6	1.5	2	THF	2	51
7	1.5	2	CH_3CN	2	46
8	1.5	2	Ethanol	2	47
9	1.5	2	1,4-Dioxane	2	56
10	1.5	2	DMF	2	Trace
11	1.5	2	DMSO	2	Trace
12	1.5	2	NMP	2	n.p.
13	1.5	2	DCM	2	n.p.
14	1.5	2	DCE	2	n.p.
15[c]	1.5	2	H_2O	2	87
16[d]	1.5	2	H_2O	2	85

[a] Conditions: **1a** (0.30 mmol) in the indicated solvent (2.0 mL) at room temperature. n.p. = No product. [b] Isolated yield. [c] Under N_2 in a sealed tube. [d] The reaction was carried out in a dark background.

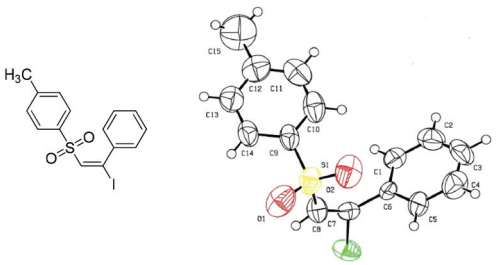
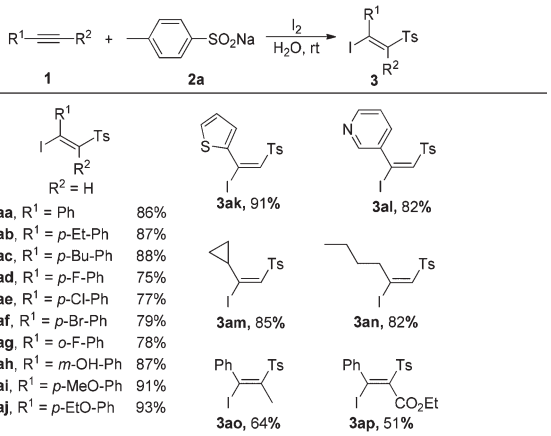


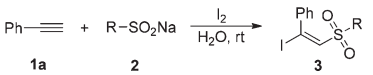
Fig. 1 X-ray crystal structure of **3aa**.

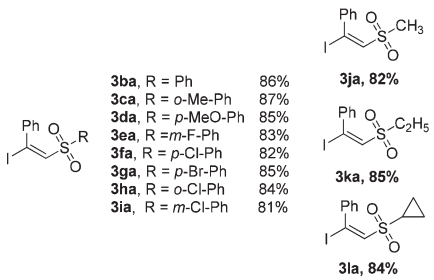
Table 2 Substrate scope of alkynes[a,b]



[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol) and I_2 (0.45 mmol) in 2.0 mL of H_2O at room temperature for 2 h. [b] Isolated yield.

Table 3 Substrate scope of sodium sulfinates[a,b]



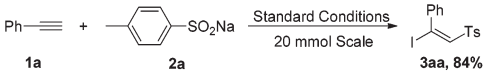


[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol) and I_2 (0.45 mmol) in 2.0 mL of H_2O at room temperature for 2 h. [b] Isolated yield.

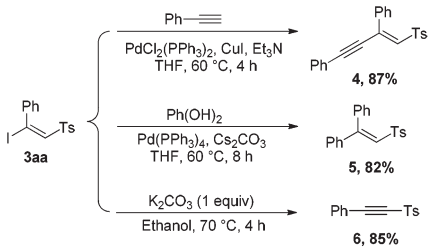
effective substituents in this transformation furnishing the corresponding products (**3fa**, **3ha**, and **3ia**) in good yields. To our delight, apart from aromatic sodium sulfinates, less reactive aliphatic sodium sulfinates such as sodium methanesulfinate, sodium ethanesulfinate, and sodium cyclopropanesulfinate were also good substrates for this reaction, giving the desired products **3ja**–**3la** in good yields. However, our attempts to employ sodium trifluoromethanesulfinate, sodium 4-nitrobenzenesulfinate, sodium 2-nitrobenzenesulfinate, and heteroaromatic sulfinate salts including sodium thiophene-2-sulfinate and sodium pyridine-3-sulfinate as substrates turned out to be ineffective, which might be caused by the instability of the corresponding sulfone radicals.

Moreover, this iodosulfonylation reaction could be scaled up to 20 mmol without a significant decrease in the yield and stereoselectivity of the product, illustrating its potential industrial applications in the future (Scheme 2).

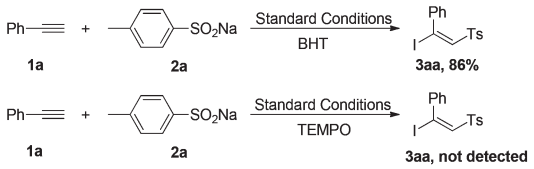
To further demonstrate the synthetic application of our developed protocol, we performed experiments using **3aa** as the starting material for further functionalization (Scheme 3). The corresponding alkynylation and arylation products **4** and



Scheme 2 Large scale experiment.



Scheme 3 Synthetic transformations of the β-iodo vinylsulfone (**3aa**).



Scheme 4 Control experiments.

5 were obtained in 87% and 82% yields *via* Sonogashira and Suzuki–Miyaura reactions, respectively.[15] We also performed dehydrohalogenation reactions of **3aa** for the synthesis of alkynyl sulfone **6**, which as we know, is a versatile and essential building block in organic and polymer chemistry.

To explore the reaction mechanism, several control experiments were conducted (Scheme 4). The existence of radical scavenger BHT did not prohibit this reaction (Scheme 4, eqn (1)). However, the reaction was completely inhibited in the presence of TEMPO (Scheme 4, eqn (2)), which indicated that this transformation should involve a radical pathway. On the basis of control experiment results and previous reports,[9–12] a possible mechanism is proposed in Scheme 5. The sulfinate sodium salt reacts with iodine to give a sulfonyl iodide intermediate that could undergo homolytic cleavage to yield a sulfonyl radical **A**. Addition of the sulfonyl radical **A** to the terminal alkyne takes place chemoselectively to form the vinyl sulfone radicals **B** and **C**. Subsequently, sulfonyl iodide, molecular iodine, or iodine radical may approach the vinyl sulfone radical **C** more readily than vinyl sulfone radical **B** to avoid a steric repulsion from the sulfonyl group to provide the difunctionalization products.[16]

In summary, we have developed an efficient metal-free synthesis of (*E*)-β-iodo vinylsulfones through iodine-promoted tandem radical reactions of alkynes and sodium sulfinates. The molecular iodine plays a dual role as both a trigger and iodine source in this radical process. Notable features of this transformation include metal-free, room temperature, water as the environmentally friendly solvent, and high regio- and stereoselectivity, which render it a powerful complement to traditional methods for the synthesis of β-halo vinylsulfone derivatives. The expansion of the synthetic application of this reaction is currently ongoing in our laboratory.

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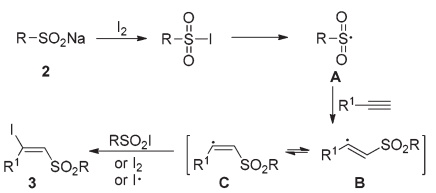

Scheme 5 Possible reaction mechanism.

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